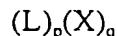


**WHAT IS CLAIMED IS:**

1. A multibinding compound of Formula (I):



5

(I)

wherein:

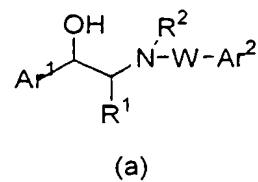
*p* is an integer of from 2 to 10;

*q* is an integer of from 1 to 20;

X is a linker; and

10 L is a ligand wherein:

one of the ligands, L, is selected from a compound of formula (a):



wherein:

Ar<sup>1</sup> and Ar<sup>2</sup> are independently selected from the group consisting of aryl, heteroaryl, cycloalkyl, substituted cycloalkyl, and heterocyclyl wherein each of said Ar<sup>1</sup> and Ar<sup>2</sup> substituent optionally links the ligand to a linker;

15 R<sup>1</sup> is selected from the group consisting of hydrogen, alkyl, and substituted alkyl, or R<sup>1</sup> is a covalent bond linking the ligand to a linker;

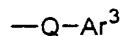
R<sup>2</sup> is selected from the group consisting of hydrogen, alkyl, aralkyl, acyl, substituted alkyl, cycloalkyl, and substituted cycloalkyl, or R<sup>2</sup> is a covalent bond linking the ligand to a linker;

20 W is a covalent bond linking the -NR<sup>2</sup>- group to Ar<sup>2</sup>, alkylene or substituted alkylene wherein one or more of the carbon atoms in said alkylene or substituted alkylene group which is optionally replaced by a substituent selected from -NR<sup>a</sup>- (where R<sup>a</sup> is hydrogen, alkyl, acyl, or a covalent bond linking the ligand to a linker), -O-, -S(O)<sub>n</sub> (where n is an integer of from 0 to 2), -CO-, -PR<sup>b</sup>- (where R<sup>b</sup> is alkyl), -P(O)<sub>2</sub>-, and -O-P(O)O- and further wherein said alkylene or

substituted alkylene group optionally links the ligand to a linker provided that at least one of Ar<sup>1</sup>, Ar<sup>2</sup>, R<sup>1</sup>, R<sup>2</sup>, or W links the ligand to a linker; and

the other ligands are independently selected from a compound of formula

(b):



(b)

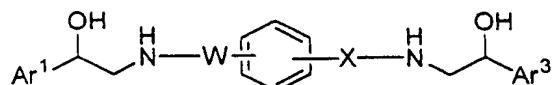
5 wherein:

Ar<sup>3</sup> is selected from the group consisting of aryl, heteroaryl, cycloalkyl, substituted cycloalkyl, and heterocyclyl;

Q, which links the other ligand to the linker, is selected from the group consisting of a covalent bond, alkylene, or a substituted alkylene group wherein 10 one or more of the carbon atoms in said alkylene or substituted alkylene group is optionally replaced by a substituent selected from -NR<sup>a</sup>- (where R<sup>a</sup> is hydrogen, alkyl, acyl, or a covalent bond linking the ligand to a linker), -O-, -S(O)<sub>n</sub>- (where n is an integer of from 0 to 2), -CO-, -PR<sup>b</sup>- (where R<sup>b</sup> is alkyl), -P(O)<sub>2</sub>-, and -O-P(O)O-; and

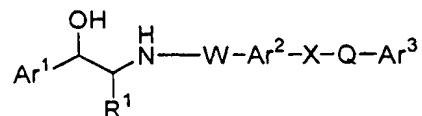
15 pharmaceutically acceptable salts thereof provided that:

(i) when the multibinding compound of Formula (I) is a compound of formula:



where Ar<sup>1</sup> and Ar<sup>3</sup> are aryl, then W and X both are not alkylene or alkylene-O-;

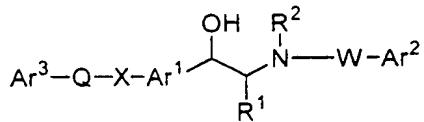
(ii) when the multibinding compound of Formula (I) is a compound of formula:



20 where Ar<sup>1</sup> is 4-hydroxy-2-methylphenyl, Ar<sup>2</sup> is aryl, Ar<sup>3</sup> is aryl or heterocyclyl, W is ethylene, Q is a covalent bond, R<sup>1</sup> is alkyl, then the linker X is not linked to the

$\text{Ar}^3$  group through an oxygen atom; and

(iii) when the multibinding compound of Formula (I) is a compound of formula:



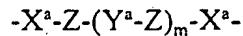
where  $\text{Ar}^1$ ,  $\text{Ar}^2$ ,  $\text{Ar}^3$ ,  $\text{R}^1$ ,  $\text{R}^2$  are as defined above.  $\text{W}$  is alkylene, and  $\text{Q}$  is a covalent bond; then  $\text{X}$  is not -alkylene-O-.

5

2. The multibinding compound of Claim 2 wherein  $q$  is less than  $p$ .

3. The multibinding compound of Claim 2 wherein each linker,  $\text{X}$ , in the multibinding compound of Formula (I) independently has the formula:

10



wherein

$m$  is an integer of from 0 to 20;

$\text{X}^a$  at each separate occurrence is selected from the group consisting of

15  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{O}-$ ,  $-\text{OC}(\text{O})-$ ,  $-\text{C}(\text{O})\text{NR}-$ ,  $-\text{NRC}(\text{O})-$ ,  $\text{C}(\text{S})$ ,  $-\text{C}(\text{S})\text{O}-$ ,  
 $-\text{C}(\text{S})\text{NR}-$ ,  $-\text{NRC}(\text{S})-$ , or a covalent bond where  $\text{R}$  is as defined below;

Z at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene,

20 cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

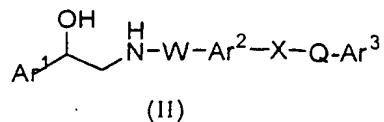
each  $\text{Y}^a$  at each separate occurrence is selected from the group consisting of

$-\text{O}-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{OC}(\text{O})-$ ,  $-\text{C}(\text{O})\text{O}-$ ,  $-\text{NR}-$ ,  $-\text{S}(\text{O})_n-$ ,  $-\text{C}(\text{O})\text{NR}'-$ ,  $-\text{NR}'\text{C}(\text{O})-$ ,  
 $-\text{NR}'\text{C}(\text{O})\text{NR}'-$ ,  $-\text{NR}'\text{C}(\text{S})\text{NR}'-$ ,  $-\text{C}(=\text{NR}')-\text{NR}'-$ ,  $-\text{NR}'-\text{C}(=\text{NR}')-$ ,  $-\text{OC}(\text{O})-\text{NR}'-$ ,  
 $-\text{NR}'-\text{C}(\text{O})-\text{O}-$ ,  $-\text{N}=\text{C}(\text{X}^a)-\text{NR}'-$ ,  $-\text{NR}'-\text{C}(\text{X}^a)=\text{N}-$ ,  $-\text{P}(\text{O})(\text{OR}')-\text{O}-$ ,  $-\text{O}-\text{P}(\text{O})(\text{OR}')-$ ,  
 $-\text{S}(\text{O})_n\text{CR}'\text{R}''-$ ,  $-\text{S}(\text{O})_n-\text{NR}'-$ ,  $-\text{NR}'-\text{S}(\text{O})_n-$ ,  $-\text{S}-\text{S}-$ , and a covalent bond; where  $n$  is 0, 1 or 2;  $\text{R}$ ,  $\text{R}'$  and  $\text{R}''$  at each separate occurrence are selected from the group

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consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, and  $X^a$  is as defined above.

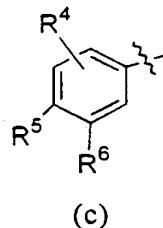
5 4. A bivalent multibinding compound of Formula (II):



wherein:

$\text{Ar}^1$  is:

(a) a phenyl ring of formula (c):



10 wherein:

$R^4$  is hydrogen, alkyl, halo, or alkoxy;

$R^5$  is hydrogen, hydroxy, halo, halo, amino, or  $\text{NHSO}_2\text{R}^a$  where  $\text{R}^a$  is alkyl;

$R^6$  is hydrogen, halo, hydroxy, alkoxy, substituted alkyl, sulfonylamino, aminoacyl, or acylamino;

15  $\text{W}$  is a bond linking the  $-\text{NR}^2-$  group to  $\text{Ar}^2$ , an alkylene or substituted alkylene chain wherein one or more of the carbon atoms in the alkylene or substituted alkylene group are optionally replaced by  $-\text{O}-$ ;

$\text{Ar}^2$  is phenyl wherein the  $\text{W}$  and the  $\text{X}$  groups are attached at the 1,2-, 1,3, and 1,4 positions of the phenyl ring; cyclohexyl optionally substituted with methyl

20 and wherein the  $\text{W}$  and the  $\text{X}$  groups are attached at the 1,3, and 1,4 positions of the cyclohexyl ring; or piperazine wherein the  $\text{W}$  and the  $\text{X}$  groups are attached at the 1,4 positions of the piperazine ring;

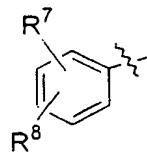
$\text{X}$  is a linker;

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Q is a covalent bond, alkylene, or a substituted alkylene group wherein one or more of the carbon atoms in said alkylene or substituted alkylene group is optionally replaced by a heteroatom such as -NR<sup>a</sup>- (where R<sup>a</sup> is hydrogen, alkyl, acyl, or a covalent bond linking the ligand to a linker), -O-, -S(O)<sub>n</sub> (where n is an integer of from 0 to 2), -CO-, -PR<sup>b</sup>- (where R<sup>b</sup> is alkyl), -P(O)<sub>2</sub>-, and -O-P(O)O- and links the ligand to a linker; and

Ar<sup>3</sup> is either:

- (i) a phenyl ring of formula (c) as defined above; or
- (ii) a phenyl ring of formula (d):



10

(d)

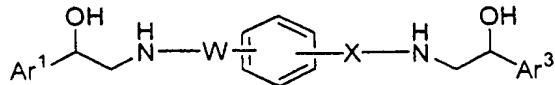
wherein:

R<sup>7</sup> is hydrogen, alkyl, alkenyl, substituted alkyl, halo, alkoxy, substituted alkoxy, hydroxy, aminoacyl, or heteroaryl; and

R<sup>8</sup> is hydrogen, halo, alkoxy, substituted alkoxy, acylamino; or

15 (iii) naphthyl, pyridyl, benzimidazol-1-yl, indolyl, 2-cyanoindolyl, carbazolyl, 4-methylindanyl, 5-(CH<sub>3</sub>CO<sub>2</sub>CH<sub>2</sub>O-)-1,2,3,4-tetrahydronaphthyl, 1H-2-oxoindole, 2,3,4-trihydrothianaphthalene, or 4-oxo-2,3-dihydrothianaphthalene; and pharmaceutically acceptable salts thereof provided that:

when the multibinding compound of Formula (I) is a compound of formula:



20 where Ar<sup>1</sup> and Ar<sup>3</sup> are aryl, then W and X both are not alkylene or alkylene-O-.

5. The bivalent multibinding compound of Claim 4, wherein:

X is -O-, -O-alkylene, -O-(arylene)-NH-(substituted alkylene), -O-(alkylene)-O-(arylene)-(alkylene)-O-(alkylene)-NH-(substituted alkylene)-,

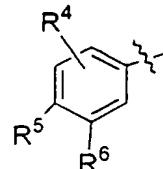
-O-(alkylene)-O-(arylene)-, -(alkylene)-(cycloalkylene)-NH-(substituted alkylene);  
and

Q is a covalent bond.

5 6. The bivalent multibinding compound of Claim 5, wherein:

$\text{Ar}^1$  is:

(a) a phenyl ring of formula (c):



(c)

wherein:

10  $\text{R}^4$  is hydrogen, methyl, fluoro, chloro, methoxy;

$\text{R}^5$  is hydrogen, hydroxy, fluoro, chloro, amino,  $-\text{NHSO}_2\text{CH}_3$ ;

$\text{R}^6$  is hydrogen, chloro, fluoro, hydroxy, methoxy, hydroxymethyl,

$-\text{CH}_2\text{SO}_2\text{CH}_3$ ,  $-\text{NHSO}_2\text{CH}_3$ ,  $-\text{NHCHO}$ ,  $-\text{CONH}_2$ ,  $-\text{NHCONH}_2$ ;

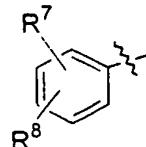
$\text{Ar}^2$  is phenyl wherein the W and the X groups are attached at the 1,4

15 position of the phenyl ring; and

$\text{Ar}^3$  is either:

(i) a phenyl ring of formula (c) as defined above; or

(ii) a phenyl ring of formula (d):



(d)

20 wherein:

$\text{R}^7$  is hydrogen, methyl, propen-2-yl, fluoro, chloro, methoxy,  $-\text{CH}_2\text{CO}_2\text{Me}$ , hydroxy,  $-\text{CH}_2\text{CONH}_2$ ,  $-\text{NHCOCH}_3$ , imidazol-1-yl, or 1-methyl-4-trifluoromethyl-imidazol-2-yl; and

R<sup>8</sup> is hydrogen, fluoro, chloro, methoxy, -CH<sub>2</sub>CO<sub>2</sub>Me, or -CONH<sub>2</sub>, or

- (iii) naphthyl, pyridyl, benzimidazol-1-yl, indolyl, 2-cyanoindolyl, carbazolyl, 4-methylindanyl, 5-(CH<sub>3</sub>CO<sub>2</sub>CH<sub>2</sub>O-)-1,2,3,4-tetrahydronaphthyl, 1H-2-oxoindole, 2,3,4-trihydrothianaphthalene, or 4-oxo-2,3-dihydrothianaphthalene.

5

7. The bivalent multibinding compound of Claim 6 wherein:

Ar<sup>1</sup> is phenyl, 4-hydroxyphenyl, 3,4-dihydroxyphenyl, 3,4-dichlorophenyl,

2-chloro-3,4-dihydroxyphenyl, 2-fluoro-3,4-dihydroxyphenyl, 2-chloro-3,5-

dihydroxyphenyl, 2-fluoro-3,5-dihydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 4-

10 hydroxy-3-hydroxymethylphenyl, 4-hydroxy-3-(HCONH-)-phenyl, 4-hydroxy-3-(NH<sub>2</sub>CO-)-phenyl, 3-chlorophenyl, 2,5-dimethoxyphenyl, 4-(CH<sub>3</sub>SO<sub>2</sub>NH-)-phenyl, 4-hydroxy-3-(CH<sub>3</sub>SO<sub>2</sub>CH<sub>2</sub>-)-phenyl, 4-hydroxy-3-(CH<sub>3</sub>SO<sub>2</sub>NH-)-phenyl, 4-hydroxy-3-(NH<sub>2</sub>CONH-)-phenyl, or 3,5-dichloro-4-aminophenyl;

W is a bond, methylene, ethylene, propylene, -(CH<sub>2</sub>)<sub>6</sub>-O-(CH<sub>2</sub>)<sub>3</sub>-,-(CH<sub>2</sub>)<sub>6</sub>-O-

15 , or -CH<sub>2</sub>CH(OH)CH<sub>2</sub>-O-;

X is -O-; -O-(CH<sub>2</sub>)<sub>4</sub>-; -O-(1,4-phenylene)-NH-CH<sub>2</sub>-CH(OH)-; -O-(CH<sub>2</sub>)<sub>10</sub>-

O-(1,4-phenylene)-(CH<sub>2</sub>)<sub>3</sub>-O-(CH<sub>2</sub>)<sub>6</sub>-NH-CH<sub>2</sub>-CH(OH)-; -O-(CH<sub>2</sub>)<sub>6</sub>-O-(1,4-

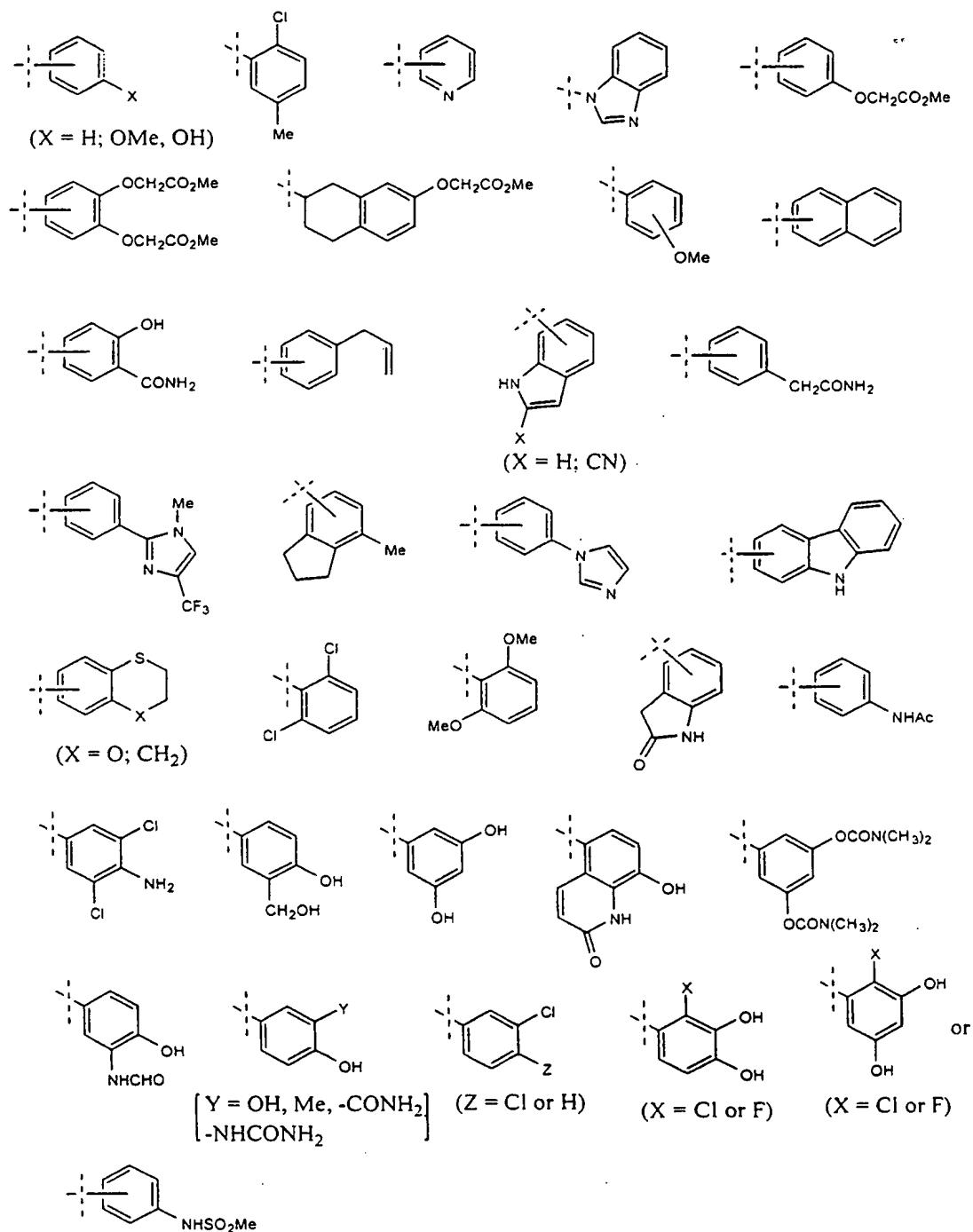
phenylene)-(CH<sub>2</sub>)<sub>3</sub>-O-(CH<sub>2</sub>)<sub>5</sub>-NH-CH<sub>2</sub>-CH(OH)-; -O-(CH<sub>2</sub>)<sub>6</sub>-O-(1,4-phenylene)-;

-CH<sub>2</sub>-(1,4-cyclohexyl)-NH-CH<sub>2</sub>-CH(OH)-; and

20 Ar<sup>3</sup> is:

25

30



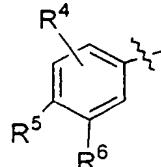
8. The bivalent multibinding compound of Claim 4, wherein:
- X is a covalent bond; and

Q is a substituted alkylene group wherein one or more of the carbon atoms in said substituted alkylene group is optionally replaced by a heteroatom such as -NR<sup>a</sup>- (where R<sup>a</sup> is hydrogen, alkyl, or acyl) or -O-.

5 9. The bivalent multibinding compound of Claim 8, wherein:

Ar<sup>1</sup> is:

- (a) a phenyl ring of formula (c):



(c)

wherein:

10 R<sup>4</sup> is hydrogen, methyl, fluoro, chloro, methoxy;

R<sup>5</sup> is hydrogen, hydroxy, fluoro, chloro, amino, -NHSO<sub>2</sub>CH<sub>3</sub>; and

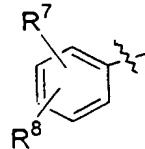
R<sup>6</sup> is hydrogen, chloro, fluoro, hydroxy, methoxy, hydroxymethyl, -CH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, -NHSO<sub>2</sub>CH<sub>3</sub>, -NHCHO, -CONH<sub>2</sub>, -NHCONH<sub>2</sub>;

Ar<sup>2</sup> is phenyl wherein the W and the X groups are attached at the 1,4

15 position of the phenyl ring; and

Ar<sup>3</sup> is either:

- (i) a phenyl ring of formula (c) as defined above; or  
 (ii) a phenyl ring of formula (d):



(d)

20 wherein:

R<sup>7</sup> is hydrogen, methyl, propen-2-yl, fluoro, chloro, methoxy, -CH<sub>2</sub>CO<sub>2</sub>Me, hydroxy, -CH<sub>2</sub>CONH<sub>2</sub>, -NHCOCH<sub>3</sub>, imidazol-1-yl, or 1-methyl-4-trifluoromethyl-imidazol-2-yl; and

R<sup>8</sup> is hydrogen, fluoro, chloro, methoxy, -CH<sub>2</sub>CO<sub>2</sub>Me, or -CONH<sub>2</sub>; or

(iii) naphthyl, pyridyl, benzimidazol-1-yl, indolyl, 2-cyanoindolyl, carbazolyl, 4-methylindanyl, 5-(CH<sub>3</sub>CO<sub>2</sub>CH<sub>2</sub>O-)-1,2,3,4-tetrahydronaphthyl, 1H-2-oxoindole, 2,3,4-trihydrothianaphthalene, or 4-oxo-2,3-dihydrothianaphthalene.

5

10. The bivalent multibinding compound of Claim 9 wherein:

Ar<sup>1</sup> is phenyl, 4-hydroxyphenyl, 3,4-dihydroxyphenyl, 3,4-dichlorophenyl,

2-chloro-3,4-dihydroxyphenyl, 2-fluoro-3,4-dihydroxyphenyl, 2-chloro-3,5-

dihydroxyphenyl, 2-fluoro-3,5-dihydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 4-

10 hydroxy-3-hydroxymethylphenyl, 4-hydroxy-3-(HCONH-)-phenyl, 4-hydroxy-3-

(NH<sub>2</sub>CO-)-phenyl, 3-chlorophenyl, 2,5-dimethoxyphenyl, 4-(CH<sub>3</sub>SO<sub>2</sub>NH-)-phenyl,

4-hydroxy-3-(CH<sub>3</sub>SO<sub>2</sub>CH<sub>2</sub>-)-phenyl, 4-hydroxy-3-(CH<sub>3</sub>SO<sub>2</sub>NH-)-phenyl, 4-hydroxy-

3-(NH<sub>2</sub>CONH-)-phenyl, or 3,5-dichloro-4-aminophenyl;

W is a bond, methylene, ethylene, propylene, -(CH<sub>2</sub>)<sub>6</sub>-O-(CH<sub>2</sub>)<sub>3</sub>-, -(CH<sub>2</sub>)<sub>6</sub>-

15 O-, or -CH<sub>2</sub>CH(OH)CH<sub>2</sub>-O-;

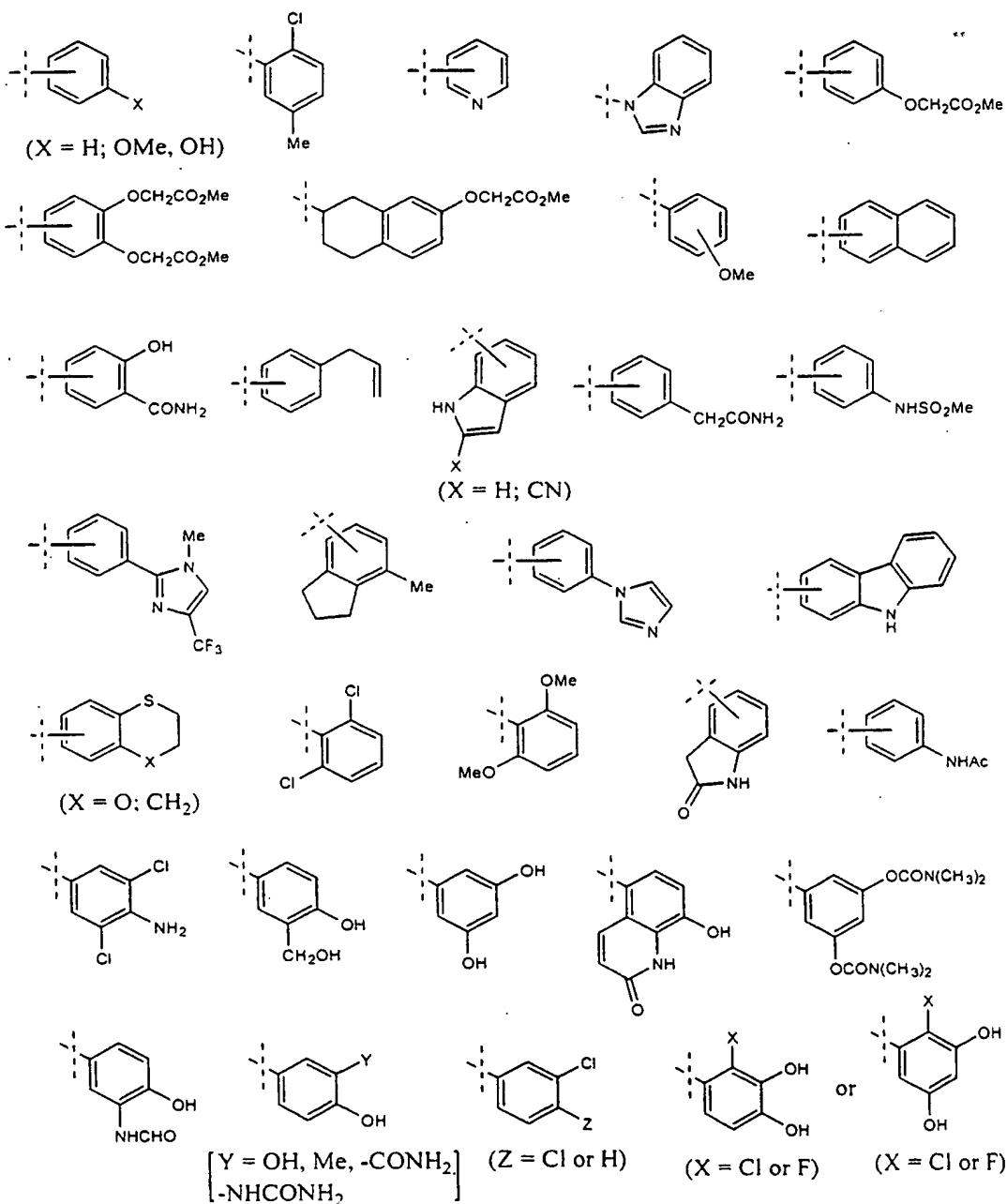
Q is -NH-CH<sub>2</sub>-CH(OH)-; -NH-CH(CH<sub>2</sub>OH)-; -CH<sub>2</sub>-NH-CH<sub>2</sub>-CH(OH)-;

-C(CH<sub>3</sub>)<sub>2</sub>-NH-CH<sub>2</sub>-CH(OH)-; -(CH<sub>2</sub>)<sub>3</sub>-NH-CH<sub>2</sub>-CH(OH)-; -(CH<sub>2</sub>)<sub>3</sub>-O-(CH<sub>2</sub>)<sub>6</sub>-NH-

CH<sub>2</sub>-CH(OH)-; -(CH<sub>2</sub>)<sub>2</sub>-NH-CH<sub>2</sub>-CH(OH)-; or -O-(CH<sub>2</sub>)-CH(OH)-CH<sub>2</sub>-NH-CH<sub>2</sub>-

CH(OH)-; and

20 Ar<sup>3</sup> is:



11. The multibinding compound of Claim 10 wherein:

Ar<sup>1</sup> and Ar<sup>3</sup> are phenyl;

W is ethylene; and

Q is -NH-CH<sub>2</sub>-\*CH(OH)- (where \* is R or S stereochemistry);

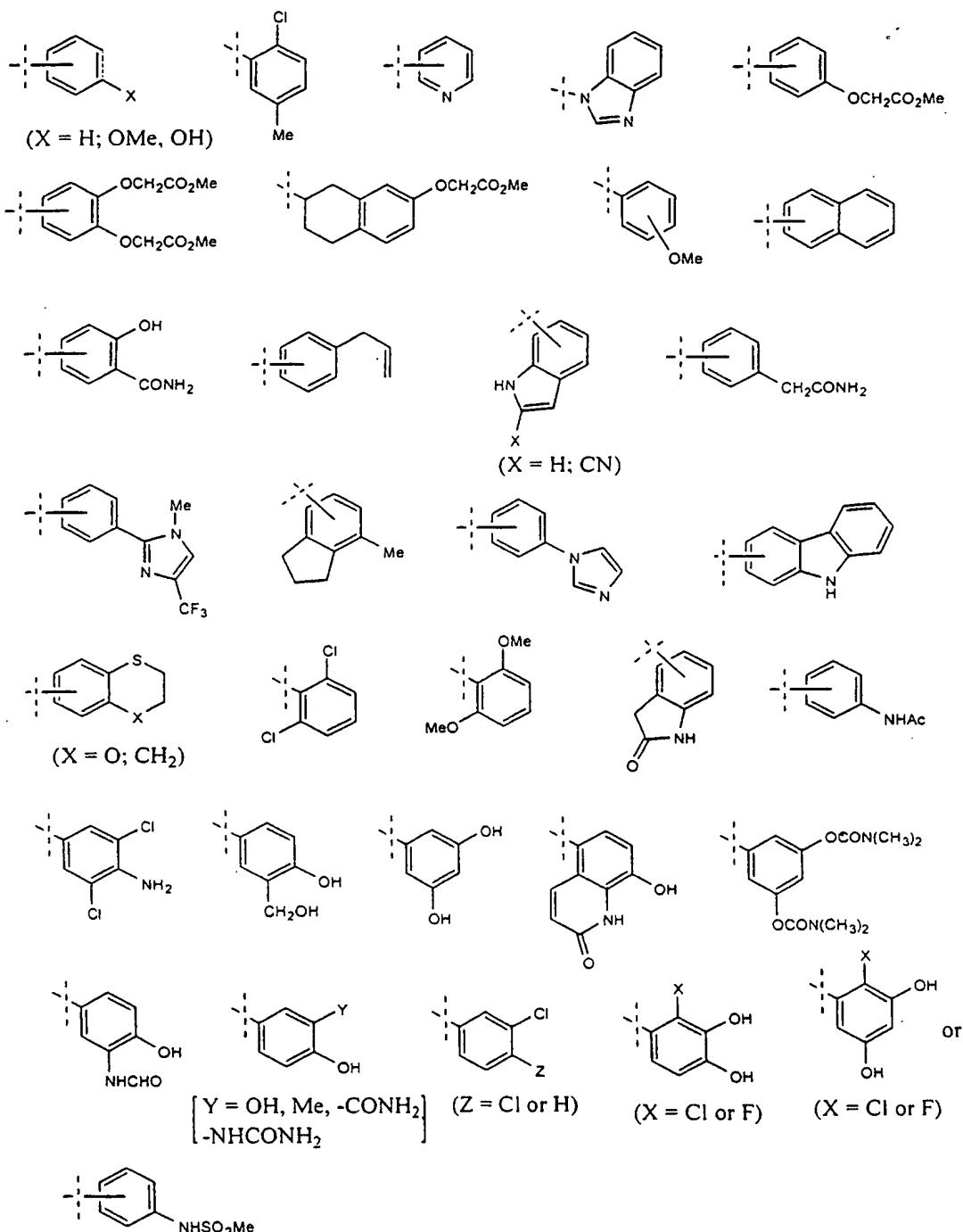
12. The bivalent multibinding compound of Claim 9 wherein:

Ar<sup>1</sup> is phenyl, 4-hydroxyphenyl, 3,4-dihydroxyphenyl, 3,4-dichlorophenyl,  
2-chloro-3,4-dihydroxyphenyl, 2-fluoro-3,4-dihydroxyphenyl, 2-chloro-3,5-  
dihydroxyphenyl, 2-fluoro-3,5-dihydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 4-  
5 hydroxy-3-hydroxymethylphenyl, 4-hydroxy-3-(HCONH-)-phenyl, 4-hydroxy-3-  
(NH<sub>2</sub>CO-)phenyl, 3-chlorophenyl, 2,5-dimethoxyphenyl, 4-(CH<sub>3</sub>SO<sub>2</sub>NH-)-phenyl,  
4-hydroxy-3-(CH<sub>3</sub>SO<sub>2</sub>CH<sub>2</sub>-)phenyl, 4-hydroxy-3-(CH<sub>3</sub>SO<sub>2</sub>NH-)-phenyl, 4-hydroxy-  
3-(NH<sub>2</sub>CONH-)-phenyl, or 3,5-dichloro-4-aminophenyl;

W is a bond, methylene, ethylene, propylene, -(CH<sub>2</sub>)<sub>6</sub>-O-(CH<sub>2</sub>)<sub>5</sub>-, -(CH<sub>2</sub>)<sub>6</sub>-  
10 O-, or -CH<sub>2</sub>CH(OH)CH<sub>2</sub>-O-;

Q is -NH-CH<sub>2</sub>-CH(OH)-CH<sub>2</sub>-O-; and

Ar<sup>3</sup> is:



13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a multibinding compound of Formula (I):

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 $(L)_p(X)_q$ 

(I)

wherein:

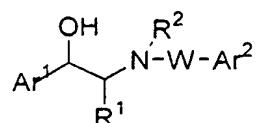
p is an integer of from 2 to 10;

5 q is an integer of from 1 to 20;

X is a linker; and

L is a ligand wherein:

one of the ligands, L, is selected from a compound of formula (a):



(a)

wherein:

10 Ar<sup>1</sup> and Ar<sup>2</sup> are independently selected from the group consisting of aryl, heteroaryl, cycloalkyl, substituted cycloalkyl, and heterocyclyl wherein each of said Ar<sup>1</sup> and Ar<sup>2</sup> substituent optionally links the ligand to a linker;R<sup>1</sup> is selected from the group consisting of hydrogen, alkyl, and substituted alkyl, or R<sup>1</sup> is a covalent bond linking the ligand to a linker;15 R<sup>2</sup> is selected from the group consisting of hydrogen, alkyl, aralkyl, acyl, substituted alkyl, cycloalkyl, and substituted cycloalkyl, or R<sup>2</sup> is a covalent bond linking the ligand to a linker;20 W is a covalent bond linking the -NR<sup>2</sup>- group to Ar<sup>2</sup>, alkylene or substituted alkylene wherein one or more of the carbon atoms in said alkylene or substituted alkylene group which is optionally replaced by a substituent selected from -NR<sup>a</sup>- (where R<sup>a</sup> is hydrogen, alkyl, acyl, or a covalent bond linking the ligand to a linker), -O-, -S(O)<sub>n</sub> (where n is an integer of from 0 to 2), -CO-, -PR<sup>b</sup>- (where R<sup>b</sup> is alkyl), -P(O)<sub>2</sub>-, and -O-P(O)O- and further wherein said alkylene or substituted alkylene group optionally links the ligand to a linker provided that at least one of Ar<sup>1</sup>, Ar<sup>2</sup>, R<sup>1</sup>, R<sup>2</sup>, or W links the ligand to a linker; and

25 the other ligands are independently selected from a compound of formula (b):

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(b)

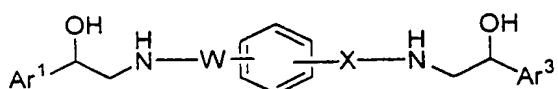
wherein:

$\text{Ar}^3$  is selected from the group consisting of aryl, heteroaryl, cycloalkyl, substituted cycloalkyl, and heterocyclyl;

- Q, which links the other ligand to the linker, is selected from the group  
 5 consisting of a covalent bond, alkylene, or a substituted alkylene group wherein  
 one or more of the carbon atoms in said alkylene or substituted alkylene group is  
 optionally replaced by a substituent selected from  $-\text{NR}^a-$  (where  $\text{R}^a$  is hydrogen,  
 alkyl, acyl, or a covalent bond linking the ligand to a linker),  $-\text{O}-$ ,  $-\text{S}(\text{O})_n-$  (where  $n$   
 is an integer of from 0 to 2),  $-\text{CO}-$ ,  $-\text{PR}^b-$  (where  $\text{R}^b$  is alkyl),  $-\text{P}(\text{O})_2-$ , and  $-\text{O}-$   
 10  $\text{P}(\text{O})\text{O}-$ ; and

pharmaceutically acceptable salts thereof provided that:

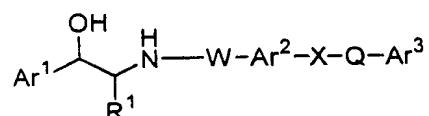
- (i) when the multibinding compound of Formula (I) is a compound of formula:



where  $\text{Ar}^1$  and  $\text{Ar}^3$  are aryl, then W and X both are not alkylene or alkylene-O-;

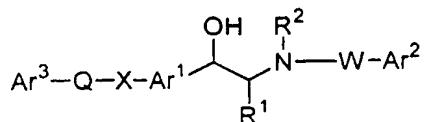
- (ii) when the multibinding compound of Formula (I) is a compound of formula:

15



where  $\text{Ar}^1$  is 4-hydroxy-2-methylphenyl,  $\text{Ar}^2$  is aryl,  $\text{Ar}^3$  is aryl or heterocyclyl, W is ethylene, Q is a covalent bond,  $\text{R}^1$  is alkyl, then the linker X is not linked to the  $\text{Ar}^3$  group through an oxygen atom; and

- 20 (iii) when the multibinding compound of Formula (I) is a compound of formula:

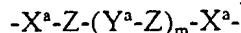


where  $\text{Ar}^1$ ,  $\text{Ar}^2$ ,  $\text{Ar}^3$ ,  $\text{R}^1$ ,  $\text{R}^2$  are as defined above.  $\text{W}$  is alkylene, and  $\text{Q}$  is a covalent bond, then  $\text{X}$  is not -alkylene-O-.

14. The pharmaceutical composition of Claim 13 wherein  $q$  is less than  $p$ .

5

15. The pharmaceutical composition of Claim 14 wherein each linker independently has the formula:



10 wherein

$m$  is an integer of from 0 to 20;

$\text{X}^a$  at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR-, -NRC(O)-, C(S), -C(S)O-, -C(S)NR-, -NRC(S)-, or a covalent bond where R is as defined below;

15  $\text{Z}$  at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

20 each  $\text{Y}^a$  at each separate occurrence is selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)<sub>n</sub>-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)NR'-, -NR'C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(X<sup>a</sup>)-NR'-, -NR'-C(X<sup>a</sup>)=N-, -P(O)(OR')-O-, -O-P(O)(OR')-, -S(O)<sub>n</sub>CR'R''-, -S(O)<sub>n</sub>-NR'-, -NR'-S(O)<sub>n</sub>-, -S-S-, and a covalent bond; where  $n$  is

25 0, 1 or 2; R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl,

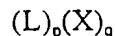
substituted alkynyl, aryl, heteroaryl and heterocyclic, and X<sup>a</sup> is as defined above.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a multibinding compound of Claim 7.

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17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a multibinding compound of Claim 10.

18. A method for treating diseases mediated by a β2 adrenergic receptor in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a multibinding compound of Formula (I):



(I)

15 wherein:

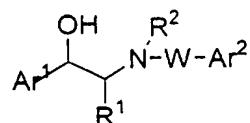
p is an integer of from 2 to 10;

q is an integer of from 1 to 20;

X is a linker; and

L is a ligand wherein:

20 one of the ligands, L, is selected from a compound of formula (a):



(a)

wherein:

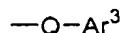
Ar<sup>1</sup> and Ar<sup>2</sup> are independently selected from the group consisting of aryl, heteroaryl, cycloalkyl, substituted cycloalkyl, and heterocyclyl wherein each of said Ar<sup>1</sup> and Ar<sup>2</sup> substituent optionally links the ligand to a linker;

25 R<sup>1</sup> is selected from the group consisting of hydrogen, alkyl, and substituted alkyl, or R<sup>1</sup> is a covalent bond linking the ligand to a linker;

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$R^2$  is selected from the group consisting of hydrogen, alkyl, aralkyl, acyl, substituted alkyl, cycloalkyl, and substituted cycloalkyl, or  $R^2$  is a covalent bond linking the ligand to a linker;

- W is a covalent bond linking the  $-NR^2-$  group to  $Ar^2$ , alkylene or
- 5     substituted alkylene wherein one or more of the carbon atoms in said alkylene or  
substituted alkylene group which is optionally replaced by a substituent selected  
from  $-NR^a-$  (where  $R^a$  is hydrogen, alkyl, acyl, or a covalent bond linking the  
ligand to a linker),  $-O-$ ,  $-S(O)_n$  (where n is an integer of from 0 to 2),  $-CO-$ ,  $-PR^b-$   
(where  $R^b$  is alkyl),  $-P(O)_2-$ , and  $-O-P(O)O-$  and further wherein said alkylene or  
10    substituted alkylene group optionally links the ligand to a linker provided that at  
least one of  $Ar^1$ ,  $Ar^2$ ,  $R^1$ ,  $R^2$ , or W links the ligand to a linker; and  
the other ligands are independently selected from a compound of formula  
(b):



(b)

wherein:

- 15      $Ar^3$  is selected from the group consisting of aryl, heteroaryl, cycloalkyl,  
substituted cycloalkyl, and heterocyclyl;

- Q, which links the other ligand to the linker, is selected from the group  
consisting of a covalent bond, alkylene, or a substituted alkylene group wherein  
one or more of the carbon atoms in said alkylene or substituted alkylene group is  
20    optionally replaced by a substituent selected from  $-NR^a-$  (where  $R^a$  is hydrogen,  
alkyl, acyl, or a covalent bond linking the ligand to a linker),  $-O-$ ,  $-S(O)_n-$  (where n  
is an integer of from 0 to 2),  $-CO-$ ,  $-PR^b-$  (where  $R^b$  is alkyl),  $-P(O)_2-$ , and  $-O-$   
 $P(O)O-$ ; and

pharmaceutically acceptable salts thereof provided that:

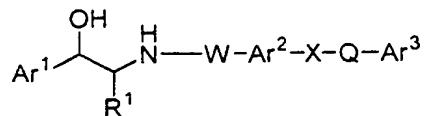
- 25    (i) when the multibinding compound of Formula (I) is a compound of formula:



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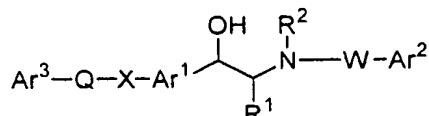
where Ar<sup>1</sup> and Ar<sup>3</sup> are aryl, then W and X both are not alkylene or alkylene-O-;

(ii) when the multibinding compound of Formula (I) is a compound of formula:



5 where Ar<sup>1</sup> is 4-hydroxy-2-methylphenyl, Ar<sup>2</sup> is aryl, Ar<sup>3</sup> is aryl or heterocyclyl, W is ethylene, Q is a covalent bond, R<sup>1</sup> is alkyl, then the linker X is not linked to the Ar<sup>3</sup> group through an oxygen atom; and

(iii) when the multibinding compound of Formula (I) is a compound of formula:



where Ar<sup>1</sup>, Ar<sup>2</sup>, Ar<sup>3</sup>, R<sup>1</sup>, R<sup>2</sup> are as defined above, W is alkylene, and Q is a covalent bond, then X is not -alkylene-O-.

19. A method for treating diseases mediated by a β2 adrenergic receptor in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a multibinding compound of Claim 7.

20. A method for treating diseases mediated by a β2 adrenergic receptor in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a multibinding compound of Claim 10.

21. The method of Claim 20 wherein the disease is a respiratory disease.

22. The method of Claim 21 wherein the disease is asthma.

23. A method for identifying multimeric ligand compounds possessing multibinding properties for  $\beta_2$  adrenergic receptor which method comprises:
- (a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;
  - 5 (b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;
  - (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified
  - 10 in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and
  - (d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties for  $\beta_2$  adrenergic receptor.

24. A method for identifying multimeric ligand compounds possessing multibinding properties for  $\beta_2$  adrenergic receptor which method comprises:
- (a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;
  - 20 (b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;
  - (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and
  - (d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties for  $\beta_2$  adrenergic receptor.

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25. The method according to Claim 23 or 24 wherein the preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b).

5

26. The method according to Claim 25 wherein the multimeric ligand compounds comprising the multimeric ligand compound library are dimeric.

27. The method according to Claim 26 wherein the dimeric ligand compounds comprising the dimeric ligand compound library are heterodimeric.  
10

28. The method according to Claim 27 wherein the heterodimeric ligand compound library is prepared by sequential addition of a first and second ligand.

15 29. The method according to Claim 23 or 24 wherein, prior to procedure (d), each member of the multimeric ligand compound library is isolated from the library.

30. The method according to Claim 29 wherein each member of the library is  
20 isolated by preparative liquid chromatography mass spectrometry (LCMS).

31. The method according to Claim 23 or Claim 24 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry,  
25 acidic linkers, basic linkers, linkers of different polarization and amphiphilic linkers.

32. The method according to Claim 31 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

30

33. The method according to Claim 32 wherein the linkers are selected to have

different linker lengths ranging from about 2 to 100Å.

34. The method according to Claim 23 or 24 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

5

35. The method according to Claim 34 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

10 36. The method according to Claim 23 or Claim 24 wherein the multimeric  
15 ligand compound library comprises homomeric ligand compounds.

37. The method according to Claim 23 or Claim 24 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

20 38. A library of multimeric ligand compounds which may possess multivalent properties for β<sub>2</sub> adrenergic receptor which library is prepared by the method comprising:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

25 (b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified  
30 in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said

linker and at least two of said ligands.

39. A library of multimeric ligand compounds which may possess multivalent properties for  $\beta_2$  adrenergic receptor which library is prepared by the method

5 comprising:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at 10 least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said 15 linker and at least two of said ligands.

40. The library according to Claim 38 or Claim 39 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic

20 linkers, basic linkers, linkers of different polarization and/or polarizability, and amphiphilic linkers.

41. The library according to Claim 40 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

25

42. The library according to Claim 41 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100 $\text{\AA}$ .

43. The library according to Claim 38 or 39 wherein the ligand or mixture of 30 ligands is selected to have reactive functionality at different sites on said ligands.

44. The library according to Claim 43 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof 5 wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

45. The library according to Claim 38 or Claim 39 wherein the multimeric 10 ligand compound library comprises homomeric ligand compounds.

46. The library according to Claim 38 or Claim 39 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

15 47. An iterative method for identifying multimeric ligand compounds possessing multibinding properties for  $\beta_2$  adrenergic receptor which method comprises:

(a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the 20 ligand or mixture of ligands which target a receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions 25 wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;

(b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties for  $\beta_2$  adrenergic receptor;

30 (c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties for  $\beta_2$

adrenergic receptor;

(d) evaluating what molecular constraints imparted multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;

5 (e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties for  $\beta_2$  adrenergic receptor to the multimeric compound or compounds found in said first iteration;

10 (f) evaluating what molecular constraints imparted enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

(g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

15 48. The method according to Claim 47 wherein steps (e) and (f) are repeated from 2-50 times.

49. The method according to Claim 48 wherein steps (e) and (f) are repeated from 5-50 times.